STUDY

Tumor Necrosis Factor Receptor–Associated Periodic Syndrome

A Novel Syndrome With Cutaneous Manifestations

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Background: Tumor necrosis factor receptor–associated periodic syndrome (TRAPS) is an inflammatory disorder characterized by prolonged episodes of periodic fever and localized inflammation and dominantly inherited mutations in *TNFRSF1A*, the gene encoding the 55-kDa tumor necrosis factor receptor. To our knowledge, the cutaneous pathologic characteristics of TRAPS have not been described previously.

Objectives: To characterize the dermatologic manifestations of TRAPS by clinical, microscopic, and molecular methods, and to investigate its immunophenotype.

Design, Setting, and Patients: At the National Institutes of Health Clinical Center, Bethesda, Md, a tertiary care referral center, 25 patients with a clinical and molecular diagnosis of TRAPS were evaluated clinically and 10 biopsy specimens of lesional skin were examined by light microscopy and immunohistochemistry. Patients were screened for mutations in *TNFRSF1A*, the gene coding for the p55 tumor necrosis factor receptor.

Main Outcome Measures: Clinical, light microscopic, and immunohistochemical features.

Results: The skin eruption usually lasted 4 to 21 days (mean, 13 days). Of 25 patients, 21 (84%) presented with migratory erythematous macules and patches and 10 (40%) had edematous dermal plaques. Conjunctivitis, characterized by pain and redness and/or periorbital edema, was present in 11 patients (44%). Most patients had their first skin eruption during the first 2 years of life. All patients had fever associated with the skin eruption. Most patients had associated abdominal pain (22 [88%]) and myalgia (20 [80%]). Other symptoms included arthralgia (13 [52%]), pleuritic chest pain (10 [40%]), and headache (17 [68%]). Microscopic examination of 10 biopsy specimens of lesional skin showed a superficial and deep perivascular and interstitial infiltrate of lymphocytes and monocytes. None of the biopsy specimens showed multinucleated macrophages or granulomatous or leukocytoclastic vasculitis. The results of immunohistochemistry showed a perivascular infiltrate of CD3+, CD4+, CD8+, CD68+, CD79a–, and CD20– cells. All the mutations were missense mutations in exons 2 through 4 of *TNFRSF1A*, directly affecting the extracellular domain of the protein.

Conclusions: TRAPS is characterized by a spectrum of dermatologic findings, including migratory patches, edematous plaques, periorbital edema, and/or conjunctivitis. TRAPS is characterized by a perivascular dermal infiltrate of lymphocytes and monocytes.

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TUMOR NECROSIS factor receptor–associated periodic syndrome (TRAPS) is a disorder characterized by prolonged episodes of fever and local inflammation caused by dominantly inherited mutations in *TNFRSF1A*, the gene encoding the 55-kDa tumor necrosis factor (TNF) receptor.[1] This nomenclature subsumes several older diagnoses, including familial Hibernian fever (FHF),[2,3] benign autosomal dominant familial periodic fever,[4] and autosomal dominant periodic fever with amyloidosis,[5] all of which share a common molecular basis. In addition to TRAPS, there are 2 other well-characterized inherited periodic fever syndromes: familial Mediterranean fever (FMF)[6,7] and the hyperimmunoglobulinemia D syndrome (HIDS) with periodic fever.[8,9] Although these syndromes have recurring episodes of fever accompanied by cutaneous and other inflammatory manifestations, they are caused by mutations in different genes.

Familial Hibernian fever was first described in 1982 in a large Irish kindred,[2] prompting the Hibernian appellation. In this family, 16 members over 3 generations exhibited periodic fevers, localized myalgia, and painful erythema inherited in a dominant pattern. In 1997, McDer-

PATIENTS AND METHODS

Twenty-five patients who were admitted to the National Institutes of Health Clinical Center, Bethesda, Md, were enrolled in a study approved by the institutional review board. All patients had documented mutations in exons 2 through 4 of *TNFRSF1A* directly affecting the extracellular domain of the p55 TNF receptor.[19] Skin lesions were classified as patches or plaques based on clinical appearance. Ten biopsy specimens of skin lesions, including erythematous macules, patches, papules, and plaques, were examined by light microscopy and immunohistochemistry. Routine morphological studies were done on 4-µm sections stained with hematoxylin-eosin. Sections from biopsy specimens were reviewed for the presence of vasculitis, interface reaction, neutrophils, mast cells, eosinophils, and plasma cells (J.R.T.).

IMMUNOPEROXIDASE STAINS

Antigen retrieval was performed as previously described.[20] Staining was performed using an automated immunostainer (Ventana Medical Systems Inc, Tucson, Ariz). Immunoperoxidase stains were done using the following antibody panel: CD3, CD8, CD68 (Dako Corp, Carpinteria, Calif), CD20, CD79a (Becton Dickinson, Mountain View, Calif), CD4 (Novocastra Labs Ltd, Newcastle upon Tyne, England).

MOLECULAR STUDIES

DNA was extracted from the peripheral blood leukocytes of each patient using standard techniques. Approximately 100 ng of genomic DNA template was used in polymerase chain reactions to amplify exons[21] and flanking intronic sequences, and mutation detection was done by fluorescent sequencing as previously described.[1]

mott et al[3] reexamined the original family described by Williamson et al.[2] They found that in addition to febrile attacks, abdominal pain and localized myalgia were frequently present. Erythematous patches, conjunctivitis, and periorbital edema were also distinctive features present in these patients.[3] Several families from different racial and ethnic backgrounds have been described who have similar clinical findings. In 1998, Mulley and coworkers[4] characterized a large Australian kindred of Scottish ancestry with similar clinical features to FHF. Smaller families of Finnish,[10] Dutch,[11] Puerto Rican[12,13] and mixed Irish, English, and German[12] descent have also been described. Although all these families had prolonged attacks (>1 week) and poor response to colchicine use, there were clinical differences between the families, most notably the presence or absence of amyloidosis and skin eruption.

In 1999, several of these families were shown to have mutations in *TNFRSF1A*.[10-13] McDermott et al[1] found 7 affected families with 6 different missense mutations in *TNFRSF1A*. Of these mutations, 5 are predicted to disrupt conserved extracellular disulfide bonds. Soluble plasma TNFRSF1A levels in patients were approximately half of the normal levels. Leukocytes bearing a C52F mutation showed little clearance of the p55 TNF receptor from the cell surface on activation and markedly reduced release of p55 into the supernatants relative to controls. The autoinflammatory phenotype may therefore result from impaired down-regulation of membrane TNFRSF1A and diminished shedding of soluble receptor. TNFR1 belongs to a family of receptors with repeating cysteine-rich extracellular motifs.[14,15] Tumor necrosis factor homotrimers induce signaling by aggregation on membrane receptors.[16] Cleavage of the extracellular domains of the TNFR1 by metalloproteases may contribute to the clearance of TNFRSF1A from the membrane, and it produces a pool of soluble receptors that compete with the membrane form.[17] TNFRSF1A is widely expressed in a variety of cells. The biologic actions of TNFRSF1A include increased expression of adhesion molecules, induction of cytokine secretion, leukocyte activation, host resistance to intracellular pathogens, angiogenesis, pyrexia, anemia, and cachexia.[18]

Although cutaneous lesions are a common manifestation of TRAPS, the cutaneous manifestations of the disease have not been well characterized. We describe herein the clinical, histologic, and immunohistochemical features of the cutaneous lesions associated with TRAPS.

Table 1. Clinical Findings in 25 Patients With TRAPS*

Findings	No. (%) of Patients
Cutaneous	
Erythematous patches†	21 (84)
Erythematous plaques	10 (40)
Ecchymotic lesions	9 (36)
Conjunctivitis and/or periorbital edema	11 (44)
Associated	
Fever	25 (100)
Myalgia	20 (80)
Abdominal pain	22 (88)
Pleuritic chest pain	10 (40)
Arthralgia	13 (52)
Headache	17 (68)
Amyloidosis	2 (8)

**TRAPS indicates tumor necrosis factor–associated periodic syndrome.*
†Sometimes serpiginous and annular lesions.

RESULTS

CLINICAL FEATURES

The clinical findings in 25 patients with TRAPS are summarized in **Table 1**. We examined 25 individuals from 16 families. There were 15 males and 10 females aged from 4 to 56 years. There were 13 children. The age of onset varied from 3 weeks to 28 years. However, 22 patients (88%) developed their first skin eruption during the first 2 years of life. The skin eruptions were exacerbated by trauma and psychological or physical stress.

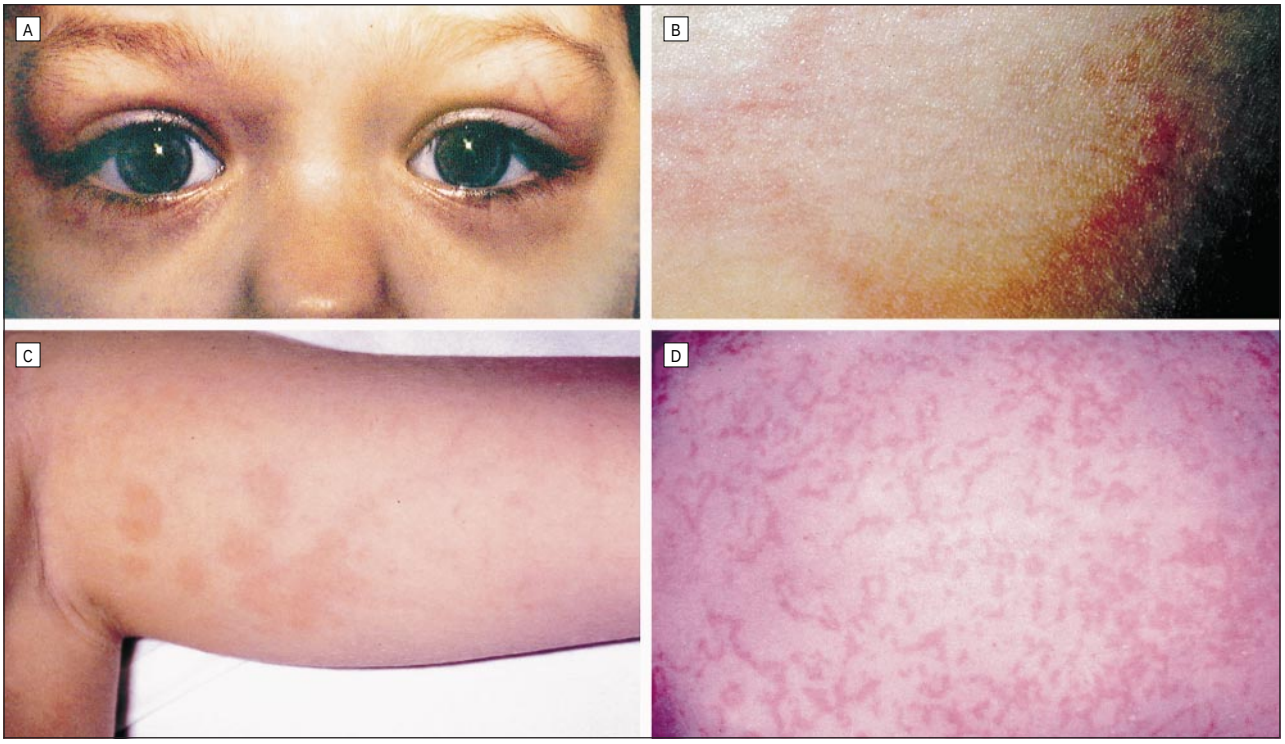

Figure 1. *The clinical spectrum of cutaneous manifestations of TRAPS (tumor necrosis factor receptor–associated periodic syndrome). A, Periorbital edema in a child. B, A large annular patch. C, Erythematous dermal macules and patches. D, Generalized erythematous serpiginous patches and plaques.*

Cutaneous manifestations were present in 21 patients (84%) during attacks (**Figure 1**). Patients presented with asymptomatic and nonscaling lesions distributed over the trunk and extremities. Most patients developed a skin eruption during a febrile attack. The skin eruption usually lasted 4 to 21 days, with a mean duration of 13 days. In addition, 10 patients (40%) exhibited edematous plaques. Lesions were from 1 to 28 cm in diameter. Large lesions tended to coalesce into annular and serpiginous patches. Most patients exhibited localized erythematous macules and patches, while others had generalized reticulated and serpiginous lesions. Migration of the lesion to the distal part of the extremity, which occurred within minutes to several days, was a distinctive feature. Nine patients (36%) stated that lesions resolved with an ecchymotic appearance. Conjunctivitis, characterized by conjunctival pain and redness and/or periorbital edema, was present in 11 patients (44%) (Figure 1).

All patients developed febrile episodes ranging in degree of severity and duration. Abdominal pain occurred in 22 patients (88%), and it was associated with nausea, vomiting, diarrhea, or constipation. Four patients were hospitalized for emergency laparotomies. Myalgia, characterized by muscle stiffness and tightness, was present in 20 patients (80%). The distal migration of the myalgia was a distinctive feature. True arthritis was rare, but arthralgia was present in 13 patients (52%). Other associated symptoms included pleuritic chest pain in 10 patients (40%) and headache in 17 patients (68%). In addition, 2 patients (8%) developed amyloidosis: one had undergone hepatic transplantation and the other had nephrotic proteinuria.[1]

HISTOLOGIC FEATURES

Microscopic evaluation of 10 biopsy specimens of erythematous macules, plaques, and annular lesions revealed a normal epidermis and both a superficial and deep perivascular and interstitial infiltrate of lymphocytes and monocytes (**Figure 2**). None of the biopsy specimens showed granulomatous or leukocytoclastic vasculitis. One biopsy specimen showed scattered neutrophils and another had a few plasma cells. There were no multinucleated macrophages, mast cells, or eosinophils present. There was no difference between different types of lesions in the intensity or type of inflammatory infiltrate. There was slightly more dermal edema present in papules and plaques.

IMMUNOPHENOTYPE

The inflammatory infiltrate in all biopsy specimens was positive for CD3 (Figure 2). There were many CD4+, CD8+, and CD68+ cells present. The results were negative for all B-cell markers tested (CD20 and CD79a). There were no immunohistologic differences among different types of lesions.

COMMENT

We found that 21 patients (87%) in this study had cutaneous manifestations. Migratory macules and patches were the most common findings. In addition, 10 patients (40%) exhibited erythematous edematous plaques. The high frequency of occurrence suggests that the cutaneous lesions are true manifestations of the syn-

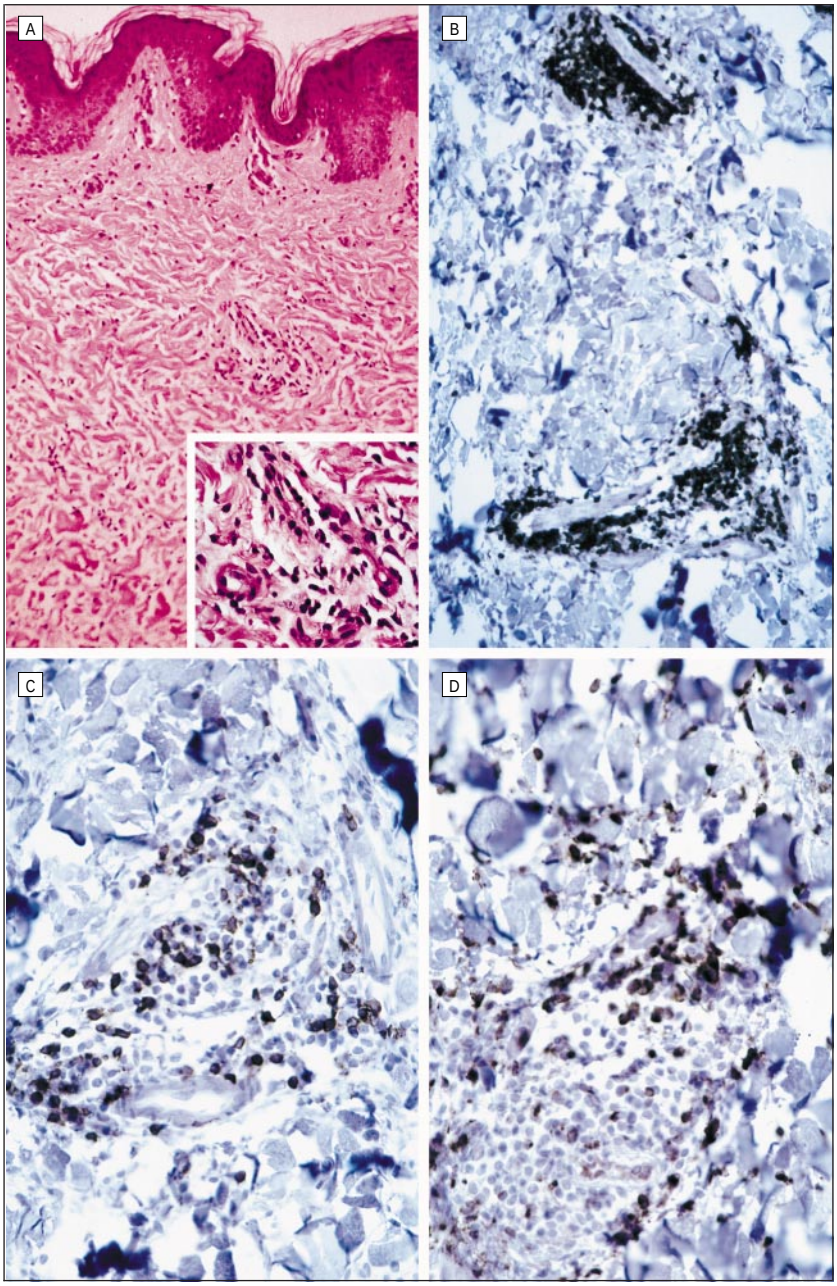

Figure 2. *Histologic and immunohistochemical findings. A, Microscopic examination shows a normal epidermis and superficial and deep perivascular infiltrate (hematoxylin-eosin, original magnification ×20). The high-magnification (original magnification ×200) inset shows small aggregates and individual lymphocytes and monocytes around vessels. B, Strongly positive CD3 cells around superficial venules. C, Perivascular infiltrate is strongly positive for CD8. D, Strongly positive CD68 cells around superficial venules. (B through D, immunoperoxidase, original magnification ×100.)*

drome. The skin lesions occurred during febrile episodes, indicating that they are part of the disease. Cutaneous manifestations usually lasted 4 to 21 days, with a mean duration of 13 days. The most common site was an extremity, where lesions began proximally and moved distally during the attack. To our knowledge, there are only a few reports in the literature about the cutaneous manifestations of FHF. In the original article of Williamson et al,[2] "painful erythemas" were described in 11 patients, and the arms were the most common site associated with underlying myalgia. In 1997, McDermott et al[3] reported skin eruptions in 11 (69%) of 16 individuals with FHF. While 9 individuals exhibited red patches, 8 had indurated lesions. We also found that cutaneous lesions were commonly associated with underlying myalgia. The myalgia moved down the extremity in conjunction with the skin lesions, affecting different muscle groups and limiting joint movement during the progression of the attack. We had the opportunity to observe the evolution of several cutaneous lesions. Early lesions consisted of solitary or groups of erythematous macules and papules. As these lesions progressed, they expanded at the periphery, coalescing into large patches or plaques. This finding of migrating large patches and plaques associated with underlying myalgia differs from HIDS, which is characterized by fixed small lesion. We also found ecchymosis in 6 patients. A previous report[3] described purpuric lesions in 3 individuals affected with FHF. In 1 individual the lesions were described as "anaphilatoid purpura" and "purpuric rash," and the diagnosis of Henoch-Schönlein purpura was made based on these dermatologic findings. Other characteristic findings in patients with TRAPS include conjunctivitis and/or periorbital edema.

Table 2. Differential Diagnosis of TRAPS, FMF, and HIDS*

	TRAPS	FMF	HIDS
Inheritance	Autosomal dominant	Autosomal recessive	Autosomal recessive
Gene	*TNFRSF1A*	*MEFV*	*MVK*
Protein	p55, CD120a	Pyrin/marenostrin	Mevalonate kinase
Disease locus	12p13.3	16p13.3	12q24
Typical ethnic backgrounds	Diverse ethnic groups	Armenian, Arab, Jewish, or Turkish	Dutch, French, or other European
Duration of attack, d	7-21	1-3	3-7
Fever	+	+	+
Abdominal pain	+	+	+
Arthralgia	+	+	+
Chest pain	+	+	–
Myalgia	+	–	–
Lymphadenopathy	–	–	+
Amyloidosis	+	+	–
Elevated IgD level, %	10	10	95
Conjunctivitis and/or periorbital edema	+	–	–
Eruption	Common	Common	Common
Distribution	Generalized	Lower leg	Extremities
Morphological characteristics	Large erythematous migratory patches or plaques; serpiginous, annular, or ecchymotic lesions	Erysipelaslike	Small erythematous macules, papules, urticaria, and nodules
Histologic characteristics	Perivascular lymphocytes and monocytes	Dermal neutrophilic infiltrate	Mild vasculitis; other Sweet-like or cellulitislike
Other dermatologic lesions	–	HSP, PAN	HSP, EED
Treatment	Corticosteroids, etanercept†	Colchicine	NSAIDs or corticosteroids (for arthritis)†

** TRAPS indicates tumor necrosis factor receptor–associated periodic syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D syndrome; plus sign, present; minus sign, absent; HSP, Henoch-Schönlein purpura; PAN, polyarteritis nodosa; EED, erythema elevatum diutinum; and NSAIDs, nonsteroidal anti-inflammatory drugs.*

† Investigational.

We found that the cutaneous histologic findings of TRAPS were nonspecific. Histologically, we could not differentiate TRAPS from a viral exanthem or serum sickness–like reaction. Biopsy specimens of individuals with TRAPS showed a superficial and deep perivascular infiltrate of lymphocytes and monocytes. We also found no histologic difference among clinically different types of lesions. To our knowledge, there are only few reports of the histologic characteristics of skin lesions associated with this syndrome. In the original report of Williamson et al,[2] the histologic findings of "painful erythema" in 2 individuals with TRAPS were a perivascular infiltrate of mononuclear cells in the dermis and swelling of vessels. In 1997, McDermott et al[3] confirmed the earlier cutaneous histologic findings of a nonspecific perivascular infiltrate in most cases. However, they also reported a case that showed upper dermal edema with telangiectasia, a low-grade lymphocytic vasculitis, increased number of mast cells, and extensive neutrophilic migration. The dermatologic characteristics in this case were not discussed. Immunofluorescence studies of a skin lesion of an individual with FHF with a history of "erythematous swelling of both legs for 15 years" showed a diffuse deposition of IgA, IgG, and C3; fibrinogen throughout the upper dermis[2]; and a fine granular deposition of IgM and C3 throughout the length of the dermal-epidermal junction.[3]

Immunohistochemical studies confirmed the T-cell phenotype in the patients in the present study. All biopsy specimens of lesional skin stained strongly positive for CD3, a pan–T-cell marker, and CD4 and CD8. In addition, we also found CD68 positive cells in the infiltrate. Therefore, TRAPS is characterized by an infiltrate of monocytes and T cells in sites of cutaneous inflammation. In contrast, cutaneous lesions of FMF are characterized by a neutrophilic infiltrate.[8] Our findings suggest that T lymphocytes and monocytes rather than neutrophils play a role in the pathogenesis of cutaneous lesions associated with TRAPS.

The differential diagnosis of TRAPS includes other syndromes characterized by periodic fever, such as FMF and HIDS. The clinical features of these 3 syndromes are compared in **Table 2**. Although these syndromes share some features, they have some distinctive characteristics. Most individuals affected with these syndromes present with initial symptoms at infancy or early childhood. The diagnosis is based on a spectrum of clinical features rather than a single characteristic. While FMF and HIDS are inherited in an autosomal recessive fashion, TRAPS is inherited in an autosomal dominant pattern. Each disorder is caused by a mutation in a different gene. The susceptibility gene for TRAPS was initially mapped to chromosome 12p13[4,22] and was subsequently found to be *TNFRSF1A*, the gene coding the 55-kDa receptor for TNF.[1] *TNFRSF1A* has a 2-kilobase (kb) coding sequence and is composed of 10 exons.[21] Five of the first 6 mutations identified were single nucleotide substitutions leading to missense changes in highly conserved extracellular cysteines, thus disrupting the stability of the extracellular domain by preventing the formation of disulfide bonds.[1] The sixth of these mutations, a threonine to methionine substitution adjacent to

an extracellular cysteine, prevents the formation of a highly conserved hydrogen bond. Eight additional mutations in *TNFRSF1A* have been identified in patients with TRAPS.[19] All 14 mutations are clustered in exons 2 through 4, directly affecting the extracellular domain of the resultant protein. Seven of the 14 result in cysteine substitutions. Only 3 mutations have been identified in more than 1 family, and mutations continue to be found in a broad range of ethnic groups.

The FMF gene, *MEFV*, has been mapped to 16p13.3. It encodes a protein named *pyrin* (referring to *pyrus*, the Greek word for fever[23]) or *marenostrin* (referring to *mare nostrum*, the Latin name of the Mediterranean Sea[24]). The gene is 15 kb long and has 10 exons. It predicts a basic protein of 781 amino acid residues[23] thought to be a leukocyte-specific regulator of inflammation[25] and is homologous to proteins of the B30.2 family.[26] A total of 26 mutations have been described in FMF.[23,24,27-32] Eleven of the mutations are in exon 10, which encodes most of the B30.2 domain, and 8 of these mutations are localized within a region of 44 nucleotides (16 amino acids). Only 1 of the mutations outside exon 10 (E148Q) is seen in several different populations, and haplotype analysis suggests a third major ancient founder effect.[27]

Hyperimmunoglobulinemia D syndrome is a disease that presents in early childhood with a median age of onset of 6 months.[9,33] The gene for HIDS is encoded on the long arm of chromosome 12 (12q24).[34] The syndrome is caused by mutations in the mevalonate kinase (*MVK*) gene. Initially, I268T, V377I, P165L, and H20P missense substitutions, and a 92-base pair deletion at the 5′ end of the gene were described.[34,35] A number of new mutations were recently presented (see http://hids.net).[33] V377I appears to be the most common mutation associated with HIDS. The relatively high frequency of this mutation, combined with the geographic concentration of cases in northern Europe, suggest a founder effect. *MVK* codes for mevalonate kinase, an enzyme that phosphorylates mevalonic acid to 5-phosphomevalonic acid in the sterol biosynthesis pathway.[36,37] Biochemical analysis of skin fibroblasts from patients harboring *MVK* mutations have demonstrated 1% to 3% of the mevalonate kinase enzymatic activity found in control fibroblasts. Patients with HIDS have elevated concentrations of mevalonic acid in their urine during, but not between, episodes of fever.[34,35]

The patient's ethnic background is also helpful in raising the suspicion of one of these syndromes. Individuals with Jewish, Armenian, Arab, Italian, or Turkish background suggest FMF.[7] To date, about half of reported cases of HIDS are in patients of Dutch ancestry; most of the remainder are from Europe (predominantly from the northern part of France), although cases have been reported in patients from Japan, Turkey, and the United States.[9,38,39] However, these syndromes can occur in patients without a typical ethnic background. Individuals with TRAPS have diverse ethnic backgrounds; however, patients of Irish and Scottish heritage are overrepresented.

Duration of attacks is another feature that differentiates FMF, TRAPS, and HIDS. Episodes of FMF are typically shorter (1-3 days) than episodes of TRAPS and HIDS. Patients with TRAPS tend to have the longest attacks, with many episodes lasting more than 1 week. It is not uncommon for patients to have episodes lasting more than 1 month and to exhibit nearly continuous inflammation. Patients with HIDS develop recurrent high fever, often preceded by headache that gradually decreases after 3 to 7 days. More than half of the patients with HIDS have a history of at least 1 attack precipitated by child immunizations. Arthralgia is common in TRAPS, FMF, and HIDS. As in FMF, arthritis in HIDS is seen with greater frequency in younger patients, tends to affect the large joints, and is characterized by a large influx of polymorphonuclear leukocytes into the synovial space.[9,40-42] Unlike FMF, HIDS arthritis frequently occurs with abdominal pain and is nondestructive; protracted arthritis in HIDS has not been observed. While oligoarticular and symmetric arthritis is seen in HIDS, monoarticular arthritis is most frequently seen in FMF. Abdominal pain is a frequent symptom in patients with all these disorders. Migratory myalgia is typically present in TRAPS but usually absent in FMF and HIDS. Patients with TRAPS complain of tightness or tension of muscle groups. Pleuritic chest pain is a frequent finding in TRAPS and FMF. Lymphadenopathy is also common is HIDS but usually absent in FMF. Hyperimmunoglobulinemia D syndrome is characterized by diffuse tender lymphadenopathy, most prominent on the neck during attacks. Splenomegaly is also observed during febrile episodes in about 50% of children. Systemic amyloidosis has been described in 4 of the first 7 families with TRAPS.[1] Amyloidosis in TRAPS is due to the deposition of serum amyloid A and can lead to renal and/or hepatic failure. In the additional families we identified, the number of families with amyloidosis has now decreased to approximately 25%. To date, there are not sufficient data to know whether the risk of amyloidosis is increased for certain *TNFRSF1A* mutations, as it is for the M694V *MEFV* mutation in FMF.[28,43,44] Amyloidosis has not been reported in HIDS.

Elevated serum IgD in individuals affected with HIDS may contribute to the pathogenesis of HIDS by potentiating the release of proinflammatory cytokines.[45] Before the identification of *MVK* as the gene that causes HIDS, the diagnostic criteria of HIDS required IgD levels exceeding 140 mg/L (14 mg/dL) on 2 occasions at least a month apart.[46] However, elevated IgD levels are not specific for HIDS. Approximately 10% to 13% of patients with TRAPS and FMF have elevated serum IgD levels. In addition, a number of other conditions have been associated with elevated serum IgD levels, including IgD multiple myeloma, Hodgkin disease, cigarette smoking, pregnancy, immunodeficiency syndromes, and recurrent infections.[9,47,48] Furthermore, some individuals with typical findings of HIDS and mutations in *MVK* do not have elevated serum IgD levels.[34] New laboratory methods, such as genetic testing for *MVK* or biochemical analysis of urine for elevated mevalonic acid, may be better to establish or confirm the diagnosis of HIDS.

We found that migratory patches and plaques are common cutaneous manifestations of TRAPS. Similarly, cutaneous lesions are common in HIDS.[47-50] In a study,[47] 79% of patients with HIDS had skin lesions dur-

ing febrile attacks. Erythematous macules were the most common cutaneous manifestation (n=15), followed by erythematous papules (n=12), urticarial lesions (n=9), and erythematous nodules (n=7). The histologic findings of cutaneous lesions associated with HIDS are varied. Most biopsy specimens showed "mild vasculitis." Other histologic findings include Sweet-like, cellulitis-like, or deep vasculitis. Henoch-Schönlein purpura and erythema elevatum diutinum have been also reported in children with HIDS.[40,51] Erysipelaslike lesions are the most distinctive cutaneous lesion associated with FMF.[52] In published studies,[53,54] the observed frequency of these lesions varies from 3% to 46%, and they have been reported to occur in 15% to 20% of children.[55-57] Patients typically exhibit erysipelaslike lesions limited to the lower extremities. Erysipelaslike lesions consist of well-demarcated, erythematous, edematous, warm plaques up to 15 cm in diameter. These lesions occur either unilaterally or symmetrically below the knee on the anterior aspect of the leg or the dorsum of the foot. Erysipelaslike lesions are histologically characterized by a dermal infiltrate of predominantly neutrophils and nuclear dust.[58] In addition, vascular inflammations, such as Henoch-Schönlein purpura and polyarteritis nodosa, have been reported to be associated with FMF. Henoch-Schönlein purpura has been reported to occur in 5% of children with FMF.[54,55,57] Purpuric lesions on the face, trunk, and extremities are also frequently found in children.[56] There have been several reports of polyarteritis nodosa with FMF.[59-63] Polyarteritis nodosa tends to occur at a younger age in FMF and is more likely to be complicated by perirenal hematoma.

The symptoms in most patients with HIDS and TRAPS respond poorly to colchicine use. The clinical response to colchicine use is an important clinical feature of FMF. About 90% to 95% of patients with FMF note marked improvement after treatment with the drug and about 75% of patients with FMF experience almost complete remission. Neutrophils in patients with FMF receiving colchicine have reduced migratory ability.[64,65] In addition, it has been shown that colchicine alters the expression of the E-selectin on vascular endothelium and L-selectin in neutrophils.[66] Both these adhesion molecules are essential for extravasation and migration to the site of inflammation. How colchicine prevents or ameliorates the attacks of FMF is still unknown. Colchicine is effective in preventing the development of amyloidosis in patients with FMF.[67] Variable results with cyclosporine, intravenous immunoglobulin, and corticosteroids have been observed in patients with HIDS. Articular manifestations in HIDS respond to either nonsteroidal anti-inflammatory drugs or corticosteroids. Preliminary results[31] using lovastatin have been encouraging for the treatment of HIDS and randomized trials are now under way. In addition, TNF inhibitors are also under investigation for HIDS. The symptoms in individuals with TRAPS respond rapidly to corticosteroid use. Nonsteroidal anti-inflammatory drugs are effective in mild attacks. Etanercept, which is a promising novel treatment for TRAPS,[68] is a bioengineered fusion protein of the p75 soluble TNF receptor (TNFR:Fc or Enbrel; Immunex Corp, Seattle, Wash) that neutralizes TNF-α. The US Food and Drug Administration approved the use of etanercept for the treatment of rheumatoid arthritis and juvenile rhematoid arthritis.[69,70]

The differential diagnosis of TRAPS also includes 2 other periodic fever syndromes in children: infantile-onset multisystem inflammatory disease (IOMID) and periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA). IOMID is a rare disorder involving a triad of arthropathy, rash, and central nervous system involvement. IOMID is differentiated from TRAPS by a neutrophilic eccrine hidradenitis, a histologic finding not present in TRAPS.[71,72] TRAPS lacks the distinctive deforming arthropathy with unique epiphyseal radiologic findings preferentially affecting large joints present in IOMID.[73] Eye involvement and neurological symptoms, including chronic meningitis, macrocephaly, and developmental delay, are common findings in IOMID and rare in TRAPS.[72-73] PFAPA is characterized by cervical adenitis, pharyngitis, aphthous stomatitis, features that rarely occur in TRAPS. Although both syndromes are characterized by periodic fever, attacks in PFAPA are shorter (4.7 days) than those in TRAPS (7-21 days).[74]

In conclusion, our data suggest that TRAPS is characterized by a spectrum of dermatologic findings, including migratory patches and plaques associated with fever and myalgia, conjunctivitis and/or periorbital edema, and ecchymotic lesions. TRAPS is characterized by a superficial and deep dermal perivascular infiltrate of monocytes and lymphocytes.

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